Heterotopic Ossification Complicating Critical Illness*

Neil C. Clements, Jr., M.D.; and Anthony E. Camilli, M.D., F.C.C.P.

Heterotopic ossification (HO), deposition of para-articular ectopic bone, is associated with musculoskeletal trauma and certain congenital and metabolic disorders. Additionally, HO may follow paralysis from diverse traumatic and nontraumatic neurologic insults. We describe three cases of HO associated with catastrophic nontraumatic respiratory illness requiring prolonged chemical paralysis and cardiorespiratory support. *(Chest 1993; 104:1526-28)*

**Neurogenic** heterotopic ossification (HO), ectopic ossification along intramuscular connective tissues, frequently occurs in extremities paralyzed by neurologic catastrophes. Although neurologists and rheumatologists are familiar with this entity, general internists and critical care specialists may not be aware of its presentation. We observed the development of HO in three previously healthy individuals who were chemically paralyzed during critical illness. The clinical presentation, differential diagnosis, and a brief discussion of therapy of HO are presented.

*From the Department of Pulmonary Medicine, Tucson Veterans Administration Medical Center (Dr. Clements), and the Department of Pulmonary Medicine (Dr. Camilli), University of Arizona Medical Center, Tucson.*

Manuscript received December 2, 1992; revision accepted March 2, 1993.

**Case Reports**

**Case 1**

A 20-year-old healthy white woman was admitted to our medical center on January 21, 1990, for systemic inflammatory response syndrome complicating pneumococcal pneumonia. Her course was complicated by septic shock, disseminated intravascular coagulation, nosocomial bacteremia, multiple electrolyte abnormalities, and pneumothoraces. Hypoxic respiratory failure was treated with pressure-controlled inverse-ratio ventilation (PCIRV) and 15 days of sedation and paralysis with vecuronium bromide.

On hospital day 16, bilateral thigh pain and knee effusions developed, associated with warm, firm, and tender quadriceps masses. Arthrocentesis yielded clear yellow fluid with 345 leukocytes (88 percent monocytes, 12 percent neutrophils). Radiographs revealed amorphous calcification consistent with early heterotopic ossification (HO) about the distal femurs (Fig 1), shoulders, and pelvis: a bone scan revealed increased activity in the same distribution.

She was treated with indomethacin and physical therapy. Radiographs on November 27, 1990 revealed well-organized heterotopic bone adjacent to the left femoral head and distal femurs associated

**Figure 1.** Flocculent calcifications (arrows) are seen about the distal femurs in case 1 (left) and 2 (center). Similar findings are seen about the glenohumeral joints in case 3 (right).
with bilateral periosteal thickening (not shown).

Case 2

A 33-year-old healthy pregnant white woman who had been receiving parenteral nutrition for hyperemesis gravidarum was admitted to University Medical Center on July 3, 1991 for staphylococcal endocarditis complicating an infected intravenous site. Her hospital course was complicated by metabolic acidosis, adult respiratory distress syndrome (ARDS), and Pseudomonas aeruginosa sepsis. Hypoxia was managed with PCIV, during which she received continuous (from hospital day 1 through 48) paralysis with vecuronium bromide.

Because of periarticular edema, radiographs of the knees were obtained on August 25, revealing changes consistent with heterotopic ossification (Fig 1). She was treated with etidronate, with full recovery except for some thigh pain on exertion. Well-formed ectopic bone was demonstrated by subsequent knee radiographs on March 24, 1992.

Case 3

A 49-year-old Hispanic woman underwent uncomplicated gynecologic surgery on April 18, 1991. Her medical history included seven pregnancies, a hysterectomy for leiomyomata, diabetes mellitus, hypertension, and ongoing tobacco use. Her medications were glyburide and an unknown antihypertensive medication.

Four days postoperatively, she developed a clinical syndrome consistent with ARDS. No pathogens were identified. Her hospitalization was complicated by multiple septic episodes, erosive gastritis, axonic encephalopathy, and severe ileus. Hypoxic respiratory failure necessitated sedation and paralysis from April 23 to June 3. Radiographic changes consistent with early HO, first evident between June 2 to 5, progressed about both glenohumeral joints (Fig 1). She recovered sufficiently to allow discharge from the hospital without any complaints referable to her HO. A chest radiograph on August 25, 1992 confirmed progression of the flocculent calcification to well-formed ectopic bone.

Figure 2 shows serial calcium-phosphorus products prior to the radiographic or clinical appearance of HO in our three patients.

Discussion

The radiographic and clinical findings in these three critically ill patients fit the syndrome of HO, a deposition of ectopic bone along connective tissues between muscle planes. In addition, a characteristic transient elevation of the alkaline phosphatase value was seen in two of our patients. Heterotopic ossification frequently develops in limbs that are paralyzed by injury to the brain or spinal cord. In addition to traumatic central nervous system injury, HO has been described following encephalitis, polio, tetanus, and other nontraumatic paralyzing illnesses. Heterotopic ossification may also complicate prolonged coma. In studies of central nervous system injury, the prevalence of HO ranged from 11 to 76.6 percent, with an interval of 32 days to 25 years between the neurologic injury and onset of HO. In contrast to patients with paralysis mediated by anatomic central nervous system injuries, the patients in our report were immobilized by therapeutic neuromuscular blockade to treat respiratory failure.

Another term, myositis ossificans (MO), is often used synonymously with HO, although it may be argued that MO describes only intramuscular ectopic bone deposition that develops at the site of trauma.
Heterotopic ossification is also distinct from metastatic calcification, which complicates a variety of illnesses that have hypercalcemia and/or hyperphosphatemia in common. By definition, the flocculent calcification of early HO (but not metastatic calcification) progresses to ossification, as was found in our three patients. The localization of the calcification solely to para-articular areas is characteristic of HO, whereas metastatic calcification typically also involves the kidneys, vascular system, skin, lungs, gastric mucosa, or cornea. Finally, the calcium-phosphorus products in our patients, although elevated, did not rise to levels generally recognized to be associated with metastatic calcification (ie, approximately 70 mg/dl) prior to the appearance of the clinical and/or radiologic abnormalities.

The pathophysiology of HO is unknown. Some authors have suggested that inciting factors are derived from denervated tissues, while others have proposed a role for genetic factors. Local circulatory, metabolic, or biochemical changes have also been stressed as important in the development of neurogenic HO.

Disrupted calcium homeostasis is a metabolic disorder that may play a role in the pathogenesis of HO. Like many who are critically ill, our patients received replacement for low total serum calcium, phosphorus, and magnesium levels early in their acute illnesses. These levels normalized during recovery from ARDS, but the depletion or repletion of calcium during critical illness might have played a role in the development of HO, even if the calcium-phosphorus product did not achieve the conventional threshold for the appearance of metastatic calcification.

The earliest manifestations of HO are typically localized swelling, pain, and decreased range of motion of involved joints. The findings may be mistaken for deep venous thrombosis, cellulitis, or acute arthritis. The radiographic abnormalities must be distinguished from neoplastic disease. Early edema, induration, erythema, and warmth may be succeeded by a well-circumscribed palpable mass, usually involving the pariarticular tissues about hips, knees, shoulders, elbows, and spine. Ankylosis of the involved joint(s) is not uncommon. Radiographic changes, periarticular flocculent calcification and local soft-tissue edema, may either precede early clinical manifestations or occur days to weeks later, and are followed by formation of well-formed trabeculated bone over 6 to 17 months. Although the effect of resolution of paralysis on established HO is unknown, spontaneous regression of early upper extremity HO has been described after resolution of the brain injury.

The treatment of HO is controversial, and a complete discussion is beyond the scope of this article. Diphosphonates have been found to decrease the rate of mineralization in HO, but not affect the amount of heterotopic bone that is ultimately formed. Nonsteroidal anti-inflammatory agents decrease the incidence and severity of HO following hip arthroplasty, but its role in neurogenic HO is unproved. Prophylactic irradiation also decreases postarthroplasty HO, but it is impractical in neurogenic HO where the frequency of its development in specific sites among the various paralytic syndromes is unclear. Surgical excision of the mature ectopic bone may be employed in symptomatic cases. We believe treatment should be individualized after consultation with orthopedic and/or rheumatologic specialists.

The clinicoradiographic syndrome of bilaterally symmetric HO developing in three patients during prolonged neuromuscular blockade (while providing cardiopulmonary support for ARDS) suggests a possible role of neuromuscular blockade as a unique form of transient symmetric paralysis. With improvements in critical care leading to increased survival after severe lung injury, HO may become a relatively frequent complication. Further understanding of the process may lead to means of detection, prevention, and treatment of HO.

References

14. van der Linden AJ. Spontaneous resolution of neurogenic heterotopic ossification. Int Orthop 1984; 8:25-7